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signaling pathways. In that case, the receptor crosstalk demonstrated here would involve two competing endogenous pathways with no need for an exogenous, infectious agent.

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Notch Signaling: A Rheostat Regulating Oligodendrocyte Differentiation?

Recent studies suggest that Notch signaling provides both instructive and inhibitory cues for oligodendroglial differentiation, depending on the developmental stage and the stimulatory ligand. In the October 17 issue of *Cell*, Hu et al. present the axonal cell adhesion molecule contactin as a functional Notch ligand, and suggest interesting potential roles for axoglial interactions in regulating oligodendroglial maturation.

The formation of myelinating oligodendrocytes from uncommitted precursors has been an area of intense study, and the phenotypic properties of developing oligodendroglia have been well characterized (Miller, 2002). Recently, the signaling events that regulate this differentiation process have begun to become uncovered. Communication with unmyelinated axons clearly plays an important role in regulating oligodendrocyte development, although an interesting remaining challenge is to explain the means by which progenitor cells migrate through vast regions of potential myelin targets prior to their final maturation. Evidence is mounting that the Notch signaling pathway plays a central role at multiple steps in the generation of mature, myelinating oligodendrocytes.

The Notch signaling pathway is exploited during development to regulate a multitude of cell fate decisions, both instructive and inhibitory. The Notch receptor, as well as its classical ligands Jagged and Delta, are transmembrane glycoproteins, indicating that Notch activation requires close cell-cell interactions, making it well suited to respond to axoglial contact. In response to ligand binding, the Notch receptor is cleaved and the intracellular domain (NICD) enters the nucleus, where it modulates the transcriptional activity of a number of genes.

Hu et al. (2003) provide evidence that contactin, also known as F3, has the potential to act as a functional ligand for the Notch receptor. Contactin is a GPI-linked cell adhesion molecule that is a member of the immunoglobin gene superfamily. Contactin is expressed by neurons, where on myelinated axons it associates with Caspr/paranodin at the paranodal domain, a site of close axoglial contact (Salzer, 2003). Hu et al. demonstrate that the adherence of the Notch-expressing OLN-93 oligodendroglial cell line to a contactin substrate is blocked by antibodies to contactin or Notch. Furthermore, immunoprecipitation experiments indicate that Notch and contactin form complexes in vivo. They also localize the contactin binding sites to specific portions of Notch's extracellular domain. Importantly, contactin binding is shown to elicit in a concentration-dependent manner the γ-secretase-mediated nuclear translocation of NICD. Notch proteolytic cleavage appears to occur at the same site in response to contactin or Jagged activation.

Ben Barres's group was the first to demonstrate a role for Notch signaling in oligodendrocyte differentiation (Wang et al., 1998). They showed that developing and mature oligodendrocytes express the Notch1 receptor and that retinal ganglion cell expression of Jagged, which is distributed along the axon, decreases developmentally in a manner that correlates with optic nerve myelination. Importantly, they also demonstrated that oligodendrocyte precursor cell (OPC) differentiation in vitro is potently inhibited by Notch signaling, suggesting that Notch-Jagged interactions play an inhibitory role in regulating the timing of CNS myelination. Recently, Genoud et al. (2002) supported this view in vivo using the Cre/lox approach to selectively eliminate Notch signaling from OPC cells, which resulted in ectopic and premature oligodendrocyte differentiation. Moreover, Givogri et al. (2002) showed that mice heterozygous for a null allele of Notch1 (homozygous mutants die before

gliogenesis initiates) display increased myelination. Together, these data argue strongly for an inhibitory role of the Notch signaling pathway in oligodendrocyte differentiation.

Recently, the Notch signaling pathway has been demonstrated to play an instructive role in the development of a variety of glial cell types, including Müller glia, radial glia, astrocytes, and Schwann cells, the myelinating cells of the peripheral nervous system (reviewed in Gaiano and Fishell, 2002). Furthermore, two papers published in *Development* this year suggest that Notch signaling might also be required for OPC specification. Grandbarbe et al. (2003) demonstrated that significantly fewer OPCs developed from neurospheres derived from embryos with a null allele of the Delta-like Notch ligand, and that this deficiency could be rescued by Jagged. Park and Appel (2003) could not detect OPCs in the spinal cord of zebrafish embryos defective in Delta, and they showed that the conditional expression of a constitutively active form of Notch promoted the generation of excess spinal cord OPCs. Thus, it appears that Notch signaling plays an instructive role in OPC generation.

Hu et al. add another interesting twist to this developing story. They show that contactin promotes the differentiation of OLN-93 cells, presumably by signaling through the Notch receptor. OLN-93 cells are transformed cells caught somewhere between OPCs and mature myelinating oligodendrocytes (Richter-Landsberg and Heinrich, 1996). These cells do not express markers of OPCs, but do express early markers of myelinating cells. The addition of contactin to OLN-93 cells resulted in a more differentiated phenotype that required the Notch signaling pathway. They also showed that greater than 70% of purified OPCs treated with contactin differentiated into oligodendrocytes, and that this response was inhibited by OPC transfection with dominant-negative components of the Notch signaling pathway. In contrast, Jagged addition, as described also by Wang et al. (1998), inhibited OPC differentiation. It remains unresolved how contactin versus Jagged activation of the Notch pathways results in a distinct cellular response, particularly because they appear to result in the identical release of NICD. Furthermore, this work needs to be resolved with data presented in Park and Appel (2003), which demonstrates that the induced expression of a constitutively active form of Notch inhibited oligodendrocyte maturation in vivo.

If a function for contactin/Notch signaling in oligodendrocyte maturation can be demonstrated in vivo, perhaps through the use of conditional alleles and inducible forms of the cre recombinase, it will paint an intricate picture of the role the Notch signaling pathway plays in CNS myelination. Notch signaling appears to play an instructive role in OPC generation in early neurodevelopment, and axonal expression of Jagged inhibits OPCs from prematurely differentiating to the myelinating phenotype. Axonal expression of Jagged decreases later in development allowing myelination to initiate. As oligodendrocytes associate with and begin to wrap axons they encounter contactin, which localizes with Caspr/paranodin to the developing paranodal domain. The Notch/contactin association may then drive the final steps of oligodendrocyte maturation. A detailed understanding of the role that the Notch signaling pathway plays in the generation of mature, myelinating oligodendrocytes might provide clues to therapeutic strategies for demyelinating disorders.

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Getting Connected

Establishing a network of blood vessels has been, for more reasons than one, an exciting field of research. In *Development*, Isogai et al. now describe in unprecedented resolution the dynamic process of angiogenesis in the trunk of the zebrafish embryo.

Despite our rapidly increasing knowledge about vasculogenesis and angiogenesis and the genes that are involved in these processes under physiological or pathological conditions, much remains to be learned about some of the more basic aspects of vessel formation. How do vessels interact with each other, how do they form initial connections, and how do they sort out arterial versus venous fates? What causes some vessels to regress, while other vessels reach out to make new connections? How, if at all, do blood flow dynamics factor